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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/52, 47/10

A1

(11) International Publication Number: WO 98/10768

(43) International Publication Date: 19 March 1998 (19.03.98)

(21) International Application Number: PCT/EP97/04945

(22) International Filing Date: 10 September 1997 (10.09.97)

(30) Priority Data:
9618974.1 11 September 1996 (11.09.96) GB

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ANTIVIRAL COMPOSITIONS

(57) Abstract

This invention relates to a topical pharmaceutical formulation suitable for use in treating virus infections of the skin and mucosa, and in particular it relates to topical formulations containing compounds having antiviral activity, particularly those active against Herpes Simplex Virus, with the exeption of aciclovir. The formulations are oil-in-water topical pharmaceutical formulations comprising a dispersed oil phase and a continuous aqueous phase comprising water, solubilised antiviral compound and at least 10 % of diethylene glycol monoethyl ether by weight of the formulation.

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ANTIVIRAL COMPOSITIONS

This invention relates to a topical pharmaceutical formulation suitable for use in treating virus infections of the skin and mucosa, and in particular it relates to topical formulations containing compounds having antiviral activity, particularly those active against Herpes Simplex Virus, with the exception of aciclovir.

Several viral infections manifest themselves on the skin surface through lesions, rashes, or other forms of skin cell disruption. Particular viral infections are Herpes Simplex Viral infections 1 and 2 which directly cause cold sores and genital sores respectively, and another herpes family virus Varicella Zoster Virus which causes chickenpox and shingles.

Several antiviral compounds have been identified as useful in the systemic treatment of antiviral infections, including but not limited to penciclovir, ganciclovir, idoxuridine, cidofovir and foscarnet Many of these compound have undesirable side effects when taken systemically thus making them unsuitable for the treatment of common, non-life threatening, viral infections such as cold sores, genital sores or shingles as described above. An ideal solution is to treat topically the affected areas of the skin either prior or during the attack. This has several advantages such as directing the drug to the affected area and limiting adverse effects to the locality of application.

However, many antiviral compounds are difficult to formulate in a suitable cream, gel, ointment or unguent due to, for example, poor solubility and/or do not readily pass through the skin to the affected area. The ability to pass through the skin is particularly important when the antiviral compound is applied during a viral attack but prior to skin cell disruption by a lesion or rash forming.

As used herein the term "antiviral compound" means any compound, except aciclovir, which has a demonstrable effect against any human viral infection. Preferred antiviral compounds are those active against HSV1 or 2 except aciclovir. Particularly preferred compound are selected from penciclovir,

famciclovir, ganciclovir, idoxuridine, foscarnet, ribivarin, and cidofovir. Particularly preferred antiviral compounds are penciclovir and cidofovir.

In addition the above properties of solubility and skin penetration it is also important that any formulation of a pharmaceutically active compound should be stable for long periods of time, should not lose its potency, should not discolour or form insoluble substances or complexes, and also should not be unduly irritating to the skin or mucosa.

We have now found that oil-in-water topical antiviral compound containing pharmaceutical formulations comprising at least 10% by weight of diethylene glycol monoethyl ether have particularly advantageous properties. In particular, such formulations exhibit enhanced efficacy together with low irritancy and good physical stability.

The present invention accordingly provides an oil-in-water topical pharmaceutical formulation comprising a dispersed oil phase and a continuous aqueous phase comprising water, solubilised antiviral compound and at least 10% of diethylene glycol monoethyl ether by weight of the formulation.

Preferably the formulation of the invention contains a maximum of 50% water.

Such a topical formulation may contain 0.075% to 10% w/w antiviral compound or a salt or an ester thereof, from 10% to 50% w/w of diethylene glycol monoethyl ether, from 15% to 50% w/w water and an oil phase. Hereafter references to antiviral compound should be understood to include also its pharmaceutically acceptable salts and esters unless the context clearly indicates otherwise.

In a preferred aspect the formulation comprises from 0.5% to 10% w/w antiviral compound, from 20% to 40% w/w of diethylene glycol monoethyl ether, from 20% to 40% w/w water together with an oil phase, whilst the most preferred formulation comprises from 1% to 5% w/w antiviral compound, from 30% to 40%

w/w of diethylene glycol monoethyl ether, from 25% to 40% w/w water together with an oil phase.

Diethylene glycol monoethyl ether is manufactured by Gatttefossé S.A., 36 Chemin de Genas, b.p. 603, 69804 Saint-Priest Cedex, France, under the tradename TRANSCUTOL™.

Penciclovir, or 2-amino-1,9-dihydro-9-[4-hydroxy-3(hydroxymethyl)butyl]-6H-purin-6-one may be made in accordance with the procedures described in US 5,075,445.

Famciclovir, or 2-[2-(2-amino-9H-purin-9-yl-ethyl]-1,3-propanediol diacetate, may be made in accordance with the procedures described in M.R. Handen et al, J. Med. Chem. 32, 1738 (1989).

Idoxuridine, or 1-(2-deoxy-B-D-ribofuranosyl)-5-iodouracil, may be made in accordance with the procedures described in GB 1,024,156.

Ganciclovir, or 2-amino-1,9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl] guanine, may be prepared in accordance with the procedures described in US 4,355,032.

Foscarnet sodium, or dihydrophosphine carboxylic acid oxide trisodium salt, may be prepared in accordance with the procedures described in US 4,215,113.

Ribavarin, or 1-β-D-ribofuran-1H-1,2,4-triazole-3-carboxamide, may be prepared in accordance with the procedures described in J.T. Witkowski et al, J. Med. Chem 15, 1150 (1972).

Cidofovir, or (S)-[[2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy] methyl]phosphoric acid may be prepared in accordance with the procedures described in US 5,142,051.

The oil phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it is desirably comprised of a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, as explained in more detail below, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so called emulsifying ointment base which forms the oil dispersed phase of the emulsions.

Emulgents and emulsion stabilisers suitable for use in the formulation of the present invention include cetyl alcohol, sodium lauryl sulphate, stearyl alcohol and polyoxyethylene alkyl ethers, such as polyoxyl stearyl ethers, for example steareth 2 and steareth 21.

The formulations of the invention may also comprise additional components in the aqueous phase, for example polyhydric alcohols such as propylene glycol. Preferably the formulations of the invention comprise from 0 to 30% by weight of propylene glycol.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of most antiviral compounds in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dialkyl esters such as diisopropyl adipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a mixed ester of 2-ethyl hexanoic acid with a blend of cetyl or stearyl alcohols known as Crodamol CAP may be used, the last three being the preferred esters. These may be used singly or in combination depending on the properties required. Alternatively, high melting point lipids

such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

A preferred formulation according to the invention comprises diethylene glycol monoethyl ether, 30-40% w/w; antiviral compound, approximately 5% w/w; cetyl alcohol 3-10% w/w; stearyl alcohol, 4-10% w/w; propylene glycol, 0-10% w/w; light mineral oil, 8-15% w/w; steareth 21, 2-5% w/w; steareth 2, 1-3% w/w; and purified water to 100% w/w.

The formulations of the invention may, if desired, include one or more pharmaceutically acceptable preservatives. However, we have found that the use of preservatives is not essential in the formulations of the invention, which finding represents an advantage of the said formulations.

The present invention further provides a method for the preparation of a topical pharmaceutical formulation, as hereinbefore defined, which comprises mixing the combination of antiviral compound, diethylene glycol monoethyl ether and water with the oil phase.

The manner of formulating the emulsion will of course vary according to the amount and nature of the constituents, but nevertheless follows known techniques in emulsion technology (see the Pharmaceutical Codex, London, the Pharmaceutical Press, 1979). For example the antiviral compound may be initially incorporated entirely in the aqueous portion where it may form a solution alone, or a mixed solution/suspension, and then emulsified with the ointment base. Alternatively where high concentrations of antiviral compound are being used, a part of the aqueous portion may be formulated as an emulsion, and the balance of the water, diethylene glycol monoethyl ether and antiviral compound added to and dispersed into the emulsion. In another technique the antiviral compound may be included in the emulsifying ointment prior to emulsification with the aqueous portion. In using these procedures, it is preferable to heat the aqueous portion and the ointment base to about 40 to 80°C, preferably 50 to 70°C, prior to emulsification which may be achieved by vigorous agitation using

for example a standard laboratory mixer. Finer dispersions of the oil phase may be obtained by homogenising or milling in a colloidal mill.

A topical formulation of the present invention may be used in the treatment or prevention of viral infections caused for example by Herpes Zoster, Herpes Varicella and Herpes simplex types I and 2, which cause diseases such as shingles, chicken pox, cold sores and genital sores. The formulation should desirably be applied to the affected area of skin from 1 to 6 times daily, preferably from 3 to 5 times.

The following example illustrates the invention and is not intended as a limitation thereof.

Example 1

Ingredient	% w/w
TRANSCUTOL™	40.0
antiviral compound	5.0
stearyl alcohol	5.0
cetyl alcohol	4.0
light mineral oil	10.2
brij 721	2.5
brij 72	2.3
Purified water	to 100

The oil phase comprising stearyl alcohol, cetyl alcohol, light mineral oil, brij 72 and brij 721 is heated to 70-75°C with mixing. Purified water is heated to 65-70°C and added to the oil phase, maintaining the temperature at 70-75°C, with mixing to form an emulsion. The mixture is maintained at a temperature of 70-75°C for approximately 5 minutes. TRANSCUTOL™ is weighed into an appropriate container and antiviral compound added with mixing to form a suspension. The antiviral compound suspension is added to the emulsion, rinsing in with a small amount of purified water. The emulsion is homogenised

for approximately 5 minutes, then made up to final batch weight with purified water. The resulting cream is cooled to ambient temperature (approximately 30°C) with continuous mixing and filled into suitable tubes which are then sealed.

Example 2

Ingredient	% w/w
TRANSCUTOL™	30.0
antiviral compound	5.0
stearyl alcohol	5.0
cetyl alcohol	4.0
light mineral oil	10.2
brij 721	2.5
brij 72	2.3
propylene glycol	10.0
Purified water	to 100

The oil phase comprising stearyl alcohol, cetyl alcohol, light mineral oil, brij 72 and brij 721 is heated to 70-75°C with mixing. Purified water is heated to 70-75°C and added to the oil phase, maintaining the temperature at 70-75°C, with mixing to form an emulsion. The mixture is maintained at a temperature of 70-75°C for approximately 5 minutes. TRANSCUTOL™ is weighed into an appropriate container and propylene glycol and antiviral compound added with mixing to form a suspension which is homogenised at 65-70°C for approximately 5 minutes. The propylene antiviral compound suspension is added to the emulsion at 50-70°C, suitably 50-55°C, rinsing in with a small amount of purified water. The emulsion is homogenised for approximately 5 minutes, then made up to final batch weight with purified water. The resulting cream is cooled to ambient temperature (approximately 30°C) with continuous mixing and filled into suitable tubes which are then sealed.

Example 3

The formulations described in Examples 1 and 2 may alternatively be prepared by the following modified procedure.

The oil phase is weighed and heated to 70-75°C with continuous slow mixing. Purified water is heated to 65-70°C. The purified water is added with propeller agitation to the suspension of aciclovir in TRANSCUTOL™. The resulting aqueous mixture is heated to 65-70°C. Whilst maintaining the temperature of the oil phase at 70-75°C, the aqueous phase is slowly added with sweep agitation for at least 5 minutes. The aqueous phase container is rinsed with purified water and the rinsings added to the main batch. The temperature of the batch is maintained at 70-75°C and the batch is homogenized for at least 5 minutes. The batch is cooled to 30-35°C with continuous sweep agitation and purified water added to adjust to final batch weight. The batch is mixed until uniform and cooled to 30°C.

CLAIMS:

1. A topical pharmaceutical formulation comprising water, solubilised antiviral compound and at least 10% of diethylene glycol monoethyl ether by weight of the formulation.

2. A topical pharmaceutical formulation as claimed in claim 1 wherein the antiviral compound is selected from penciclovir, famciclovir, ganciclovir, idoxuridine, foscarnet, ribivarin and cidofovir.

3. A topical pharmaceutical formulation as claimed in claim 2 wherein the antiviral compound is penciclovir

4. A topical pharmaceutical formulation as claimed in any preceding claim wherein the formulation contains a maximum of 50% water.

5. A topical pharmaceutical formulation as claimed in any preceding claim wherein the formulation comprises 0.075% to 10% w/w antiviral compound or a salt or an ester thereof, from 10% to 50% w/w of diethylene glycol monoethyl ether, from 15% to 50% w/w water and an oil phase.

6. A topical pharmaceutical formulation as claimed in any preceding claim wherein the formulation comprises 0.5% to 10% w/w antiviral compound.

7. A topical pharmaceutical formulation as claimed in any preceding claim wherein the formulation comprises from 20% to 40% w/w of diethylene glycol monoethyl ether.

7. A topical pharmaceutical formulation as claimed in any preceding claim wherein the formulation comprises from 20% to 40% w/w water together with an oil phase.

8. A topical pharmaceutical formulation as claimed in any preceding claim wherein the formulation comprises from 1% to 5% w/w antiviral compound.

9. A topical pharmaceutical formulation as claimed in any preceding claim wherein the formulation comprises from 30% to 40% w/w of diethylene glycol monoethyl ether.

10. A topical pharmaceutical formulation as claimed in any preceding claim wherein the formulation comprises from 25% to 40% w/w water together with an oil phase.

11. A topical pharmaceutical formulation as claimed in any preceding claim wherein the formulation comprising an oil phase comprised of a mixture of at least one emulsifier with one or both of a fat or an oil.

12. A topical pharmaceutical formulation as claimed in any preceding claim wherein the formulation further comprises a polyhydric alcohol.

13. A topical pharmaceutical formulation as claimed in any preceding claim wherein the polyhyric alcohol is propylene glycol and is present at from 1 to 30% by weight.

14. A topical pharmaceutical formulation comprising diethylene glycol monoethyl ether, 30-40% w/w; antiviral compound, approximately 5% w/w; cetyl alcohol 3-10% w/w; stearyl alcohol, 4-10% w/w; propylene glycol, 0-10% w/w; light mineral oil, 8-15% w/w; steareth 21, 2-5% w/w; steareth 2, l-3% w/w; and purified water to 100% w/w.

15. A method for the preparation of a topical pharmaceutical formulation claimed in any preceding claim, which method comprises mixing the combination of antiviral compound, diethylene glycol monoethyl ether and water with the oil phase.

16. A method of treating a patient suffering from a viral infection of the skin or mucosa by applying a formulation according to any one of claims 1-14 to the affected area from 1-6 times daily.

17. Use of an antiviral agent selected from the group consisting of penciclovir, famciclovir, ganciclovir, idoxuridine, foscarnet, ribivarin and cidofovir in the preparation of a topical medicament comprising at least 10% of diethylene glycol monoethyl ether by weight of the formulation.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 97/04945

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/52 A61K47/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 095 813 A (PROCTER & GAMBLE) 7 December 1983 see claims	1-17
A	WO 95 35095 A (YISSUM) 28 December 1995 see claims	1-17
E	WO 97 34607 A (GLAXO) 25 September 1997 see the whole document	1,4-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
18 December 1997	15.01.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No.
PC., EP 97/04945

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 16 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr ial Application No
PCT/EP 97/04945

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 95813 A	07-12-83	AU 1527983 A	08-12-83
		CA 1200497 A	11-02-86
		DK 248783 A	02-12-83
		JP 59031709 A	20-02-84
WO 9535095 A	28-12-95	US 5540934 A	30-07-96
		AU 2977695 A	15-01-96
		EP 0804160 A	05-11-97
WO 9734607 A	25-09-97	NONE	

Form PCT/ISA/210 (patent family annex) (July 1992)